AWARD NUMBER: W81XWH-16-1-0436

TITLE: Treatment of Sleep Apnea in Patients With Cervical Spinal Cord Injury

PRINCIPAL INVESTIGATOR: M. Safwan Badr, M.D.

CONTRACTING ORGANIZATION: Wayne State University
Detroit, MI 48201

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Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

During this research period, approval from all required regulatory agencies was received. New staff were hired and trained, and the research database was established and built. These activities completed Major Task 1. Participant recruitment started on 06/12/2017 after receiving HRPO approval. Participants are being actively recruited and enrolled for Specific Aim 1. We have screened 11 participants and 3 have completed the study. Demographic and questionnaire data are being entered into the RedCap database.

15. SUBJECT TERMS

Nothing listed

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INTRODUCTION:

This proposal aims to investigate potential therapeutic approaches for sleep-disordered breathing (SDB) in patients with chronic cervical spine injury (>6 months post-injury). Our central hypothesis is that cervical SCI is associated with frequent episodes of hypoxia, resulting in chronic intermittent hypoxia (CIH), recurrent arousals from sleep, and increased peripheral chemoreceptor activity. To test our central mechanistic hypothesis, we propose a series of experiments to investigate the following Specific Aims: (1): To test the hypothesis that patients with cervical SCI will demonstrate greater magnitude of LTF following EH during sleep, compared to patients with thoracic SCI. This aim will be accomplished by measuring the effect of acute episodic hypoxia on post-hypoxic ventilation and upper airway mechanics in both groups. (2): To test the hypothesis that dampening peripheral chemoreceptor activity in patients with cervical SCI and central SDB with supplemental O2 will reduce central respiratory events and decrease respiratory variability during sleep. This aim will be accomplished by providing supplemental O2 to patients with cervical SCI and central SDB. (3): To test the hypothesis that administration of trazodone, in patients with cervical spinal cord injury and central SDB will decrease respiratory-related arousals and the central apneas index, compared to placebo. To accomplish this aim, trazodone, a sedating serotonergic agent will be administered to cervical SCI patients with central SDB. The proposed experiments will identify therapeutic approaches for the treatment of central SDB in patients with cervical spinal cord injury, which can potentially be generalized to patients with other neuromuscular disease and across the continuum of SDB in the general population.

1. KEYWORDS:

sleep disordered breathing, spinal cord injury, chronic intermittent hypoxia, long term facilitation, episodic hypoxia, trazodone, central sleep disordered breathing

2. ACCOMPLISHMENTS:

The progress during this annual reporting period includes completion of Major Task 1: Obtain Required Approvals, Study Set Up and Staff Training. Regulatory documents and research protocols were prepared for the study and the research protocols were approved by the:

VA CIC – 06/20/2016
WSU IRB – 08/23/2016
DMC Research office – 02/24/2017
DoD HRPO – 06/09/2017

All research staff who will interact with human subjects or their identifiable information have completed Human Subjects Protection training. The first annual continuing review for the IRB was submitted and approved on 07/12/2017. New staff have been hired and trained on all study procedures. RedCap has been established as the research database. The database has been built and is ready to use.

Additionally, we have started Major Task 2: Participant Recruitment, Informed Consent, Screening Visit and Performance of Studies for Specific Aim 1. In order to complete Aim 1 research staff screen potential subjects for inclusion and exclusion criteria and obtain

basic information through a phone interview. At the first study visit, informed consent is obtained and the participants complete questionnaires about health and sleep. Visit 2 is a baseline overnight sleep study including polysomnography (PSG) and determination of the apneic threshold. Following the baseline sleep study, each subject will be studied in two separate sessions, in random order, one for episodic hypoxia and one as a sham run. Both studies will be conducted during sleep. During the episodic hypoxia (EH) study, the subjects will undergo 30 minutes of baseline monitoring followed by 15 episodes of one minute of EH with supplemental CO_2 to maintain isocapnia. In the sham session, the subject will undergo an identical study (sham) without EH, followed by 30 minutes of recovery. Following the hypoxia exposure, the ventilatory and upper airway resistance changes will be measured to assess the occurrence of long-term facilitation on ventilation and upper airway mechanics. To determine the presence of long-term facilitation (LTF), ventilation, chemical stimuli and upper airway resistance will be compared to the first pre-hypoxia control period, after each hypoxic period, and at the recovery period following termination of episodic hypoxia at 10, 20 (main measurement time point) and 30 minutes after the 15^{th} hypoxic exposure (recovery).

Participant recruitment started on 06/12/2017 after receiving HRPO approval. Participants are being actively recruited and enrolled for Specific Aim 1. We have screened 11 participants and 3 have completed the study. Demographic and questionnaire data are being entered into the RedCap database.

During the next reporting period we will continue recruiting participants to meet our goal of having 20 participants complete the LTF studies. Meeting this goal will complete Specific Aim 1. We will begin recruitment for Specific Aim 2.

3. IMPACT:

Nothing to Report

4. CHANGES/PROBLEMS:

Recruitment of participants started on 06/12/2017 immediately after receiving HRPO approval which was granted 6 months after the original projection. As outlined in the original Statement of Work, completion of SA 1 and and all other related tasks will require 12 months from the time of HRPO approval. An updated Quad Chart is attached.

5. PRODUCTS:

Nothing to Report

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

Name:	M. Safwan Badr, M.D.
Project Role:	PI
Researcher Identifier:	
Nearest person month worked:	4
Contribution to Project:	Dr. Badr performed work related to the preparation, conduct, and administration of all aspects of the project.

Funding Support:	
Name:	Abdulghani Sankari, M.D., Ph.D.
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	4
Contribution to Project:	Dr. Sankari performed work related to the oversight of regulatory document preparation and gaining approval from all required regulatory agencies.
Funding Support:	

Name:	Lawrence Horn, M.D.
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	1
Contribution to Project:	Dr. Horn performed work related to helping staff obtain DMC approval and recruitment from DMC.
Funding Support:	

Name:	Harry Goshgarian, Ph.D.
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	1
Contribution to Project:	Dr. Horn performed work related to project oversight
Funding Support:	

Name:	Hossein Yarandi, Ph.D.
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	1
Contribution to Project:	Dr. Horn performed work related to database set up
Funding Support:	

Name:	Sarah Vaughan, Ph.D.
Project Role:	Study Coordinator
Researcher Identifier:	
Nearest person month worked:	13
Contribution to Project:	Dr. Vaughan performed work related to the preparation of all regulatory documents and submissions to regulatory agencies. She also performed work related to research staff training, database set-up, participant recruitment, and data analysis.
Funding Support:	

Name:	Andria Caruso
Project Role:	Research Assistant
Researcher Identifier:	
Nearest person month worked:	12
Contribution to Project:	Ms. Caruso performed work related to participant recruitment, and performing PSG and overnight intervention studies.
Funding Support:	

Name:	Waleed Ayesh, M.D.
Project Role:	Research Assistant
Researcher Identifier:	
Nearest person month worked:	9
Contribution to Project:	Dr. Ayesh performed work related preparation of regulatory documents, participant recruitment, and scoring sleep studies.
Funding Support:	

7. SPECIAL REPORTING REQUIREMENTS:

An updated Quad Chart is being submitted as an attachment.

8. APPENDICES:

None

Project Title: Treatment of sleep apnea in patients with cervical spinal cord injury

PI: M. Safwan Badr, M.D., M.B.A

Log Number: SC150201

Award Number: W81XWH-16-1-0436

Q1. Project Description:

Total Award Amount Requested $: 2,851,225.00

Start Date – End Date : *(08/01/2016) - (07/31/2020)*

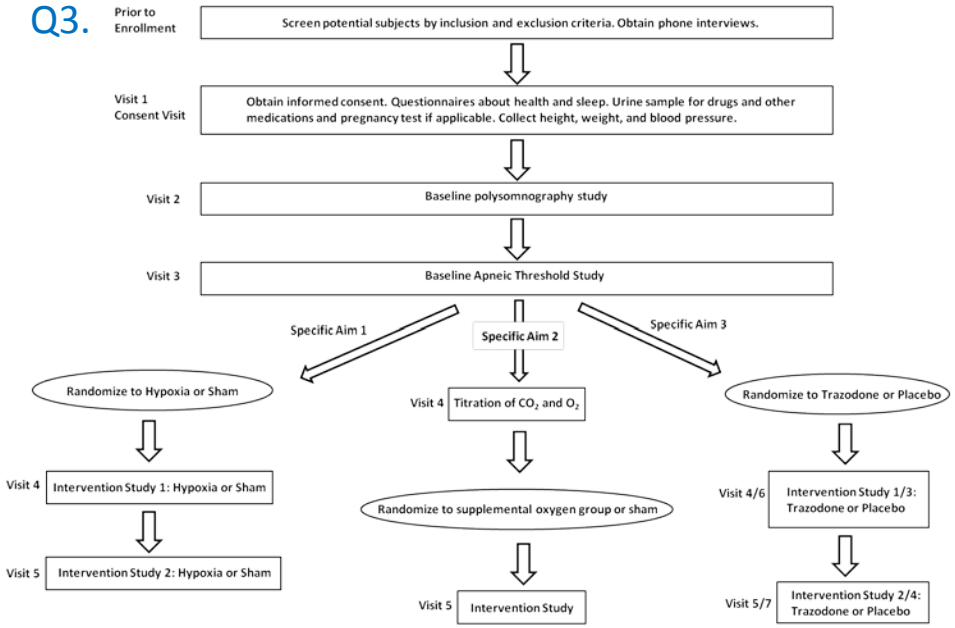
Describe Key Research Aims:

• Aim 1: To test the hypothesis that patients with cervical SCI will demonstrate greater magnitude of long-term facilitation (LTF) following episodic hypoxia during sleep, compared to patients with thoracic Spinal cord injury. The primary endpoints will be the change in V_T and V_E in the recovery period.

• Aim 2: To test the hypothesis that dampening peripheral chemoreceptor activity in patients with cervical SCI and central SDB with supplemental O2 will reduce central respiratory events and decrease respiratory variability during sleep. The primary endpoints will be the change in CO_2 reserve compared to baseline.

• Aim 3: To test the hypotheses that: a)Acute administration of trazodone in patients with cervical SCI and central SDB will decrease respiratory-related arousals and central apnea index compared to placebo, and b) Chronic (1 week) administration of trazodone will result in decreased propensity to central apnea, evidenced by widening of the CO_2 reserve. The primary endpoints will be the change in respiratory related arousals.

Q3.



Q2. Scientific Innovations:

The development of central SDB in patients with cervical SCI may seem predictable until we ask *why* these patients develop this condition. While one would expect SDB among SCI patients with diurnal hypoventilation, we have noted this phenomenon in patients with normal daytime ventilation and oxygenation who are not using opiates for pain and have no evidence of impaired phrenic or hypoglossal nerve activity. However, the most innovative aspect of our proposal is that we will gain an understanding of the mechanistic underpinnings of central SDB in cervical SCI patients, leading to identification of novel therapeutic targets or a more individualized use of existing therapies that can be tested among other SDB patients as well. Another innovation is the use of in-lab enhanced polysomnography with quantitative measurements of air pressure and airflow. Our methods will allow us to quantify ventilation, measure the severity of inspiratory flow limitation, characterize upper airway mechanics, and evaluate chemical stimuli. Our goal is to:

1. Identify therapeutic strategies that could be tested in large clinical trials.
2. Improve quality of life among patients with cervical SCI who also experience central SDB.

Q4. Timelines:

Tasks	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
Complete all regulatory reviews and finalize study components	■				
Aim 1: Subject Recruitment		■	■		
Aim 1: 20 Participants Complete Aim 1			■	■	
Aim 2: Subject Recruitment		■	■	■	
Aim 2: 20 Participants Complete Aim 2			■	■	
Aim 3: Subject Recruitment				■	■
Aim 3: 20 Participants Complete Aim 3				■	■
Complete Data Analysis and Report Results				■	■